

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
30 October 2003 (30.10.2003)

PCT

(10) International Publication Number
WO 03/089434 A2(51) International Patent Classification⁷: C07D 487/04,
A61K 31/4985, A61P 35/00 // (C07D 487/04, 241:00,
235:00)

(21) International Application Number: PCT/US03/12222

(22) International Filing Date: 21 April 2003 (21.04.2003)

(25) Filing Language: English

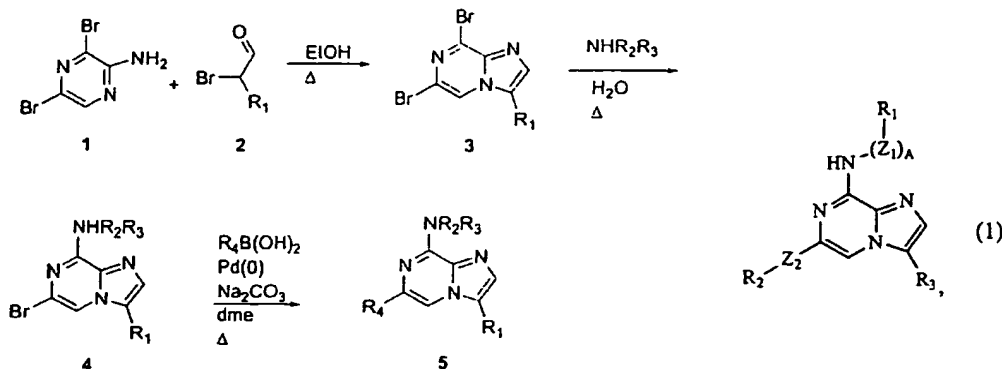
(26) Publication Language: English

(30) Priority Data:
60/374,213 19 April 2002 (19.04.2002) US(71) Applicant: CELLULAR GENOMICS, INC. [US/US];
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fin Road South, Bloomfield, CT 06002 (US).(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ,
VC, VN, YU, ZA, ZM, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that reportFor two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZO[1,2-a]PYRAZIN-8-YLAMINES METHOD OF MAKING AND METHOD OF USE THEREOF



(57) Abstract: A novel composition comprises a compound of Formula 1 the pharmaceutically acceptable salts, hydrates, solvates, crystal forms, diastereomers, prodrugs, or mixtures thereof. The composition is of particular utility in the treatment of kinase-implicated disorders.

Imidazo[1,2-a]pyrazin-8-ylamines, Method of Making, and Method of Use Thereof

BACKGROUND

This invention relates to certain imidazo[1,2-a]pyrazin-8-ylamines and related compounds, which when appropriately substituted are modulators of kinase activity. This invention also relates to pharmaceutical compositions comprising such compounds, and to the use of such compounds in treating a variety of kinase-associated disorders. Additionally, this invention relates to the use of such compounds as probes for the identification of kinases of therapeutic interest.

One of the central post-translational control elements in eukaryotic signal transduction is the phosphorylation of the hydroxyl moiety of serine, threonine, or tyrosine. The phosphorylation state of a given protein can govern its enzyme activity, stability, protein-protein binding interactions, and cellular distribution. Phosphorylation and dephosphorylation is thus a "chemical switch" that allows the cell to transmit signals from the plasma membrane to the nucleus, and to ultimately control gene expression. Although the exact mechanisms of signal transduction have yet to be elucidated, kinases are involved in the control of cell metabolism, growth, differentiation, and apoptosis. These signaling mechanisms affect the onset of cancer, metabolic disorders (for example diabetes), inflammation, immune system disorders, and neurodegeneration. Certain kinases have been implicated in cell proliferation and carcinogenesis. For example, many human cancers are caused by dysregulation of a normal protein (e.g., when a proto-oncogene is converted to an oncogene through a gene translocation). Because kinases are key regulators they are ideal drug design targets.

Inhibitors of kinases are among the most important pharmaceutical compounds known. Tyrosine kinase inhibitors are useful in inhibiting T-cell proliferation, and thus they are useful as immunosuppressive agents for the prevention or treatment of graft rejection following transplant surgery and for the prevention or treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis. Other tyrosine kinase

inhibitors have been described, for example, in U.S. Patent No. 5,593,997 to Dow et al. Erlotinib (CP-358774) teach a quinazoline derivative under development as an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor for treatment of solid tumors including non-small cell lung cancer (NSCLC), pancreatic cancer, breast cancer, and neck cancer. Gleevec and Imatinib (STI-571), from Novartis, are tyrosine kinase inhibitors indicated for treatment of chronic myelogenous leukemia (CML), prostate tumors, and gastrointestinal stromal tumors, among others. AstraZeneca is developing gefitinib (ZD-1839; Iressa), an inhibitor of epidermal growth factor receptor 1 (EGFR1) tyrosine kinase, for the potential treatment of cancers which over-express EGF receptors, including non-small cell lung cancer (NSCLC) and other solid tumors such as breast tumors. CEP-1347 (Cephalon Inc.) is an indolcarbazole choline acetyltransferase inhibitor and c-jun N-terminal kinase inhibitor for treatment of Alzheimer's disease, Parkinson's disease, and AIDS-related peripheral neuropathy. Cephalon is also developing CEP-701, an orally active tyrosine kinase inhibitor for the potential treatment of prostate and other cancers. A PDGF receptor tyrosine kinase inhibitor (SU-101, leflunomide) is being investigated for treatment of various cancers and rheumatoid arthritis. Sugen has also investigated the anti-cancer effects of the FLK-1 tyrosine kinase inhibitor Semaxanib, particularly for colorectal and lung cancers, leukemia, Kaposi's sarcoma, and others.

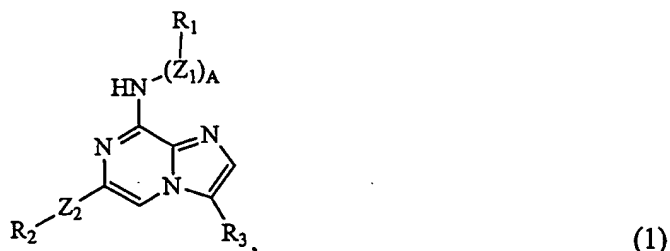
Serine/threonine kinase inhibitors are also pharmaceutically important. Eli Lilly is developing LY333531 (ruboxistaurin), an inhibitor of protein kinase C beta, for treatment of diabetic macular edema and diabetic retinopathy. Flavopirodol (Aventis) is a synthetic flavonoid inhibitor of cyclin-dependent kinases, is under development for treatment of mantle cell lymphoma (MCL) and fludar refractory chronic lymphocytic leukemia (CLL). One Raf kinase inhibitor (BAY-43-9006, Bayer) is in development for treatment of solid tumors and myeloid leukemia, and another (ISIS 5132, Isis) is being investigated for treatment of ovarian cancer. Several p38 mitogen-activated protein kinase inhibitors (VX-745, VX-702, and VX-850, Vertex, and SCIO-469, Scios) have been investigated for treatment of inflammation, rheumatoid arthritis, and myelodysplastic syndrome (MDS).

Highly selective, cell-permeable modulators of one or more individual kinases would thus be useful in the treatment of various kinase-implicated disorders. Such compounds would also be useful for the systematic investigation of the cellular function of one or more kinases, and thus, would provide invaluable tools for the
5 identification of various kinases of therapeutic interest.

The compounds most closely related structurally to those described herein are a series of imidazolopyrazines described in WO 02/060492, as JAK inhibitors for the treatment of immune disorders. A series of piperazinyimidazo[1,2a]pyrazines are described by Lumma *J. Med. Chem.* 1983, 26, 357-363 as displaying affinity for α -
10 adrenergic receptors. Other imidazo[1,2-a]pyrazines have been reported to be useful as bronchodilators and phosphodiesterase inhibitors (see, for example, *Bioorg. Med Chem.* 1999, pages 1059-1065). Effects on pulmonary hypertension have also been reported (see, for example, *J. Cardiovasc. Pharmacol.* 1998, volume 32, no. 2, pages 213-219). The compounds described in these publications are not within the scope of
15 the present invention.

SUMMARY

In one embodiment, this invention is directed to a composition comprising a compound of Formula 1:



- 5 the pharmaceutically acceptable salts, hydrates, solvates, crystal forms, diastereomers, prodrugs, or mixtures thereof,

wherein R₁ is hydrogen; cyclo-(C₃-C₆ alkyl)-methyl; straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains may form a 3 to 7 member heteroalkyl or alkyl ring; sulfonamide; C₁-C₆ alkoxy; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; mono- or di(C₁-C₆ alkyl)amino; mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl); or phenyl or heteroaryl ring which may be unsubstituted, or mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, sulfonamide, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl); and,

R₂ is straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains may form a 3-7 member heteroalkyl or alkyl ring; cyclo-(C₃-C₆ alkyl)-methyl; C₁-C₆ alkoxy, except when Z₂ is phenylene and A is 0 and R₁ is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen, or when Z₂ is phenylene and A is 1, Z₁ is -C(R₄)(R₅)- wherein m is 1, 2, or 3 and R₁ is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen, or when Z₂ is -C(R₇)(R₈)- wherein n is 1, 2, or 3, each occurrence of R₇ and R₈ is independently straight or branched chain C₁-C₆ alkyl or halogen and R₂ is C₁-C₆ alkoxy or phenyl substituted with nitro; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; or phenyl or heteroaryl which may be unsubstituted, mono-, di- or

trisubstituted with one or more of hydroxy, nitro (except when Z_2 is phenylene and A is 0 and R_1 is straight or branched chain C_1 - C_7 alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C_1 - C_6 alkoxy, or halogen, or when A is 1 and Z_1 is $-C(R_4)(R_5)-$ wherein m is 1, 2, or 3, and R_1 is straight or

5 branched chain C_1 - C_7 alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C_1 - C_6 alkoxy, or halogen, or when Z_2 is phenylene and A is 1 and Z_1 is $-C(R_4)(R_5)-$ wherein m is 1, 2, or 3 and R_1 is straight or branched chain C_1 - C_7 alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C_1 - C_6 alkoxy, or halogen, or when Z_2 is $-C(R_7)(R_8)-$ wherein n is

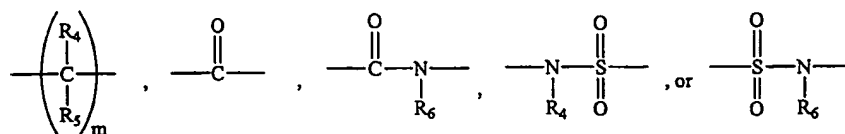
10 1, 2, or 3, each occurrence of R_7 and R_8 is independently straight or branched chain C_1 - C_6 alkyl or halogen and R_2 is C_1 - C_6 alkoxy or phenyl substituted with nitro), cyano, amino, halogen, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, (C_1-C_6) -alkyl-oxy- (C_1-C_6) alkoxy, mono- or di(C_1 - C_6 alkyl)amino, or amino(C_1 - C_6 alkyl); phenoxy phenyl

15 where each phenyl may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, (C_1-C_6) -alkyl-oxy- (C_1-C_6) alkoxy, mono- or di(C_1 - C_6 alkyl)amino, or amino(C_1 - C_6 alkyl); phenyl or heteroaryl piperazine where the phenyl or heteroaryl ring may be independently

20 unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, (C_1-C_6) -alkyl-oxy- (C_1-C_6) alkoxy, mono- or di(C_1 - C_6 alkyl)amino, or mono- or di(C_1 - C_6 alkyl)amino(C_1 - C_6 alkyl);

R_3 is hydrogen; straight or branched chain C_1 - C_7 alkyl, in which the branched alkyl chains may form a 3-7 member heteroalkyl or alkyl ring;

Z_1 is



5 wherein

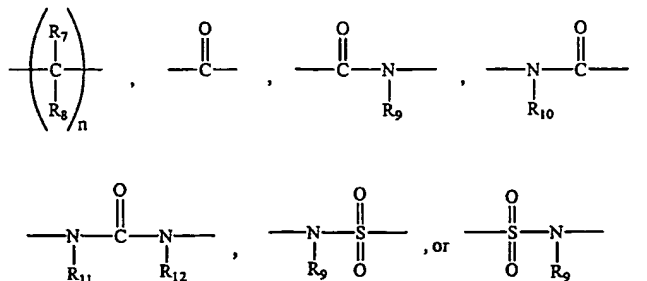
A is 0 or 1;

each occurrence of R_4 and R_5 is independently hydrogen, straight or branched chain C_1 - C_6 alkyl, sulfonamide, or halogen;

m is 0, 1, or 2; and

10 R_6 is hydrogen; straight or branched chain C_1 - C_6 alkyl; phenyl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, $(C_1$ - C_6)-alkyl-oxy- $(C_1$ - C_6)alkoxy, mono- or di- $(C_1$ - C_6 alkyl)amino, or amino $(C_1$ - C_6 alkyl); or heteroaryl which may be
15 unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, $(C_1$ - C_6)-alkyl-oxy- $(C_1$ - C_6)alkoxy, mono- or di- $(C_1$ - C_6 alkyl)amino, or amino $(C_1$ - C_6 alkyl); and

Z_2 is a divalent linking group selected from para-phenylene, meta-phenylene,
20 ortho-phenylene, naphthylene,



wherein

each occurrence of R_7 and R_8 is independently straight or branched chain C_1 - C_6 alkyl, sulfonamide, or halogen;

n is 1, 2, or 3; and

5 R_9 - R_{12} are each independently hydrogen; straight or branched chain C_1 - C_6 alkyl; phenyl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, (C_1 - C_6)-alkyl-oxy-(C_1 - C_6)alkoxy, mono- or di(C_1 - C_6 alkyl)amino, or amino(C_1 - C_6 alkyl); or heteroaryl which may be unsubstituted, mono-, di- or
10 trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, (C_1 - C_6)-alkyl-oxy-(C_1 - C_6)alkoxy, mono- or di(C_1 - C_6 alkyl)amino, or amino(C_1 - C_6 alkyl).

In another embodiment, a pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula 1 and a pharmaceutically acceptable
15 carrier.

In still another embodiment, a method of treating a kinase-implicated disorder in a mammal comprises administration to the mammal of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula 1 and a pharmaceutically acceptable carrier.

20 In another embodiment, a method for identifying a kinase comprises contacting an organism, cell, or preparation comprising the kinase with a compound of Formula 1, and detecting modulation of the kinase activity.

BRIEF DESCRIPTION OF THE DRAWINGS:

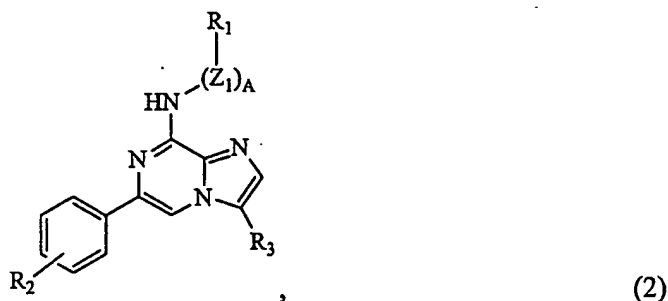
FIGURE 1 is a schematic illustrating one synthesis of the present compounds.

25 FIGURE 2 is a schematic illustrating another synthesis of the present compounds.

DETAILED DESCRIPTION

The compounds of Formula 1 are novel compounds belonging to the family of imidazo[1,2-a]pyrazines. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula 1 with a kinase (i.e., one or
5 more kinases) results in modulation of the activity of the kinase(s). The compounds of Formula 1 are thus expected to have therapeutic application in mammalian kinase-implicated conditions. As used herein, "modulation" refers to a change in kinase activity as a direct or indirect response to the presence of a compound of Formula 1, relative to the activity of the kinase in the absence of the compound. The change may
10 be an increase in activity or a decrease in activity, and may be due to the direct interaction of the compound with the kinase, or due to the interaction of the compound with one or more other factors that in turn affect kinase activity. For example, the presence of the compound may increase or decrease kinase activity by directly binding to the kinase, by causing (directly or indirectly) another factor to
15 increase or decrease the kinase activity, or by (directly or indirectly) increasing or decreasing the amount of kinase present in the cell or organism.

In one preferred embodiment, novel imidazo[1,2-a]pyrazines may comprise compounds of general Formula 2:



the pharmaceutically acceptable salts, hydrates, solvates, crystal forms, diastereomers, prodrugs, or mixtures thereof.

In Formula 2, R₁ is hydrogen; cyclo-(C₃-C₆ alkyl)-methyl; straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains are allowed to also form a 3-7 member heteroalkyl or alkyl ring; sulfonamide; C₁-C₆ alkoxy; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl); or phenyl or heteroaryl ring which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, sulfonamide, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl).

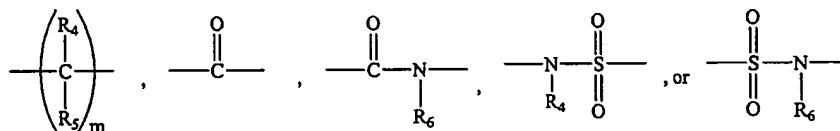
R₂ in Formula 2 is straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains are allowed to also form a 3-7 member heteroalkyl or alkyl ring; cyclo-(C₃-C₆ alkyl)-methyl; C₁-C₆ alkoxy except when A is 0 and R₁ is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen, or when A is 1 and Z₁ is -C(R₄)(R₅)- wherein m is 1, 2, or 3 and R₁ is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; phenyl or heteroaryl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, (except when A is 0 and R₁ is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen, or when A is 1 and Z₁ is -C(R₄)(R₅)- wherein m is 1, 2, or 3 and R₁ is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl

substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen)cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl- oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, amino(C₁-C₆ alkyl); phenoxy phenyl where each phenyl may be independently unsubstituted,
 5 mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl); or phenyl or heteroaryl piperazine where the phenyl or heteroaryl ring may be independently unsubstituted, mono-, di- or trisubstituted with one or
 10 more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl).

R₃ in Formula 2 may be hydrogen; straight or branched chain C₁-C₇ alkyl, in
 15 which the branched alkyl chains can also form a 3-7 member heteroalkyl or alkyl ring.

A in Formula 2 is 0 or 1.

Z₁ in Formula 2 is



wherein

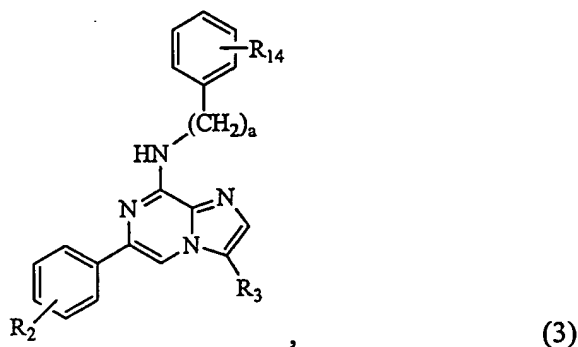
20 each occurrence of R₄ and R₅ is independently hydrogen, straight or branched chain C₁-C₆ alkyl, sulfonamide, or halogen;

m is 1, 2, or 3; and

R₆ is hydrogen; straight or branched chain C₁-C₆ alkyl; phenyl, which may be unsubstituted, mono-, di- or trisubstituted with one or more of
 25 hydroxy, nitro, cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl); or heteroaryl, which may be

unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl).

- 5 In another preferred embodiment, the novel imidazo[1,2-a]pyrazines comprise compounds of general Formula 3:



the pharmaceutically acceptable salts, hydrates, solvates, crystal forms, diastereomers, prodrugs, or mixtures thereof.

- 10 In Formula 3, a is 0, 1, 2 or 3. R₁₄ is hydrogen; cyclo-(C₃-C₆ alkyl)-methyl; straight or branched chain C₁-C₆ alkyl, in which the branched alkyl chains may form a 3-7 member heteroalkyl or alkyl ring; sulfonamide; C₁-C₆ alkoxy; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; mono- or di(C₁-C₆ alkyl)amino, mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl); or phenyl or heteroaryl ring, which may be unsubstituted, mono-, di- or
- 15 trisubstituted with one or more of hydroxy, nitro, cyano, amino, sulfonamide, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl).

- R₂ in Formula 3 is straight or branched chain C₁-C₆ alkyl, in which the branched alkyl chains may form a 3-7 member heteroalkyl or alkyl ring; cyclo-(C₃-C₆ alkyl)-
- 20 methyl; C₁-C₆ alkoxy except where R₁ is hydrogen, C₁-C₆ alkoxy, or phenyl substituted with nitro; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; phenyl or heteroaryl, which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or

amino(C₁-C₆ alkyl); phenoxy phenyl, in which each phenyl may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro (except where R₁ is hydrogen, C₁-C₆ alkoxy, or phenyl substituted with nitro), cyano, amino, halogen, sulfonamide, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl); or phenyl or heteroaryl piperazine, in which the phenyl or heteroaryl ring may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl).

R₃ is hydrogen; straight or branched chain C₁-C₆ alkyl, in which the branched alkyl chains may form a 3-7 member heteroalkyl or alkyl ring.

As used herein, when any variable occurs more than one time in the formulas, its definition on each occurrence is independent of its definition at every other occurrence. In accordance with the usual meaning of "a" and "the" in patents, reference to "a" kinase or "the" kinase is inclusive of one or more kinases.

By "heteroaryl" is meant aromatic systems containing at least one heteroatom, for example, oxygen, nitrogen, sulfur, and the like, as well as combinations comprising at least one of the foregoing heteroatoms. Suitable heteroaryl groups include, for example (as numbered from the linkage position assigned priority 1), 2-pyridyl, 3-pyridyl, 4-pyridyl, 2,3-pyrazinyl, 3,4-pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,3-pyrazolinyl, 2,4-imidazolinyl, isoxazolinyl, oxazolinyl, thiazolinyl, thiadiazolinyl, tetrazolyl, and the like.

By "heteroalkyl" is meant an aliphatic ring containing at least 1 carbon atom in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, or nitrogen, and the like, as well as combinations comprising at least one of the foregoing heteroatoms.

By "sulfonamide" is meant -S(O)₂N- in either S-linked or N-linked orientation, wherein the nitrogen atom can be unsubstituted; or mono- or disubstituted with cyclo-

(C₃-C₆ alkyl)-methyl or straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains may form a 3-7 member alkyl or heteroalkyl ring.

By "piperazine" is meant unsubstituted piperazine, as well as piperazines independently substituted on 1-4 carbon atoms with hydroxy, cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, mono- or di(C₁-C₆ alkyl)amino, mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl), or sulfonamide.

By "C₁-C₆ alkyl" is meant straight or branched chain alkyl groups or cycloalkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl, and the like. Preferred C₁-C₆ alkyl groups are methyl, ethyl, propyl, butyl, cyclopropyl, cyclopropylmethyl, cyclohexyl, cycloheptyl, and norbornyl.

By "C₁-C₆ alkoxy" is meant an alkyl group of the indicated number of carbon atoms attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. Preferred alkoxy groups herein are C₁-C₄ alkoxy groups.

The term "halogen" includes fluorine, chlorine, bromine, and iodine.

If the compounds of Formula 1 have asymmetric centers, then Formula 1 includes all of the optical isomers and mixtures thereof. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high-pressure liquid chromatography (HPLC) column. Where a compound of Formula 1 exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers, and includes all tautomeric forms of the compound.

Representative compounds of the present invention, which are encompassed by Formula 1, include, but are not limited to their pharmaceutically acceptable acid addition salts. Non-toxic "pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, such as hydrochlorate, phosphate, diphosphate, 5 hydrobromate, sulfate, sulfinate, nitrate, or like salts; or salts with an organic acid, such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate such as acetate, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and like salts. Similarly, pharmaceutically acceptable cations include, but are not limited to 10 sodium, potassium, calcium, aluminum, lithium, and ammonium.

In addition, if the compound of Formula 1 is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, it may be produced by dissolving the free base in a suitable organic 15 solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts encompassed by Formula I.

Prodrugs of the compounds of Formula 1 are also within the scope of the present 20 invention, for example acylated prodrugs of the compounds of Formula 1. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable acylated and other prodrugs of the compounds encompassed by Formula 1.

Methods for obtaining the compounds described herein are known to those of 25 ordinary skill in the art, suitable procedures being described, for example, in the references cited herein.

As mentioned above, it is believed that the interaction of the compounds of Formula 1 with one or more kinases results in modulation of the activity of the one or more kinases. Suitable kinases include but are not limited to tyrosine kinases and 30 serine/threonine kinases, which may be classified as including the AGC group (cyclic nucleotide regulated family) of protein kinases, which includes the cyclic nucleotide

regulated protein kinase family (e.g., PKA and PKG), the diacylglycerol-activated/phospholipid-dependent family protein kinase C family (e.g., PKC), the PKA and PKC-related family (e.g., RAC and Akt), the kinases that phosphorylate G protein-coupled receptors family, the budding yeast AGC-related protein kinase
5 family, the kinases that phosphorylate ribosomal protein S6 family, the budding yeast DBF2/20 family, the flowering plant PVPK1 protein kinase homolog family, and other AGC related kinase families.

The CaMK (calcium calmodulin dependent) group of protein kinases includes kinases regulated by Ca^{2+} /CaM and close relatives family, the KIN1/SNF1/Nim1
10 family, and other related CaMK related kinase families. The CMGC group (named because it includes the cyclin-dependent kinases) includes the cyclin-dependent kinases (e.g., CDKs) and close relatives family, the ERK (e.g., MAP) kinase family, the glycogen synthase 3 (e.g., GSK3) family, the casein kinase II family, the Clk family and other CMGC kinases.

15 The PTK group of protein kinases includes protein-tyrosine kinases that may be nonmembrane-spanning or membrane-spanning tyrosine kinases. The PTK group of protein kinases includes the Src family, the Tek/Atk family, the Csk family, the Fes (Fps) family, the Abl family, the Syk/ZAP70 family, the Ttk2/Jak1 family, the Ack family, the focal adhesion kinase (Fak) family, the epidermal growth factor receptor
20 family, the Eph/Elk/Eck receptor family, the Axl family, the Tie/Tek family, the platelet-derived growth factor receptor family, the fibroblast growth factor receptor family, the insulin receptor family, the LTK/ALK family, the Ros/Sevenless family, the Trk/Ror family, the DDR/TKT family, the hepatocyte growth factor receptor family, the nematode Kin15/16 family and other PTK kinase families.

25 The OPK group (other protein kinases) includes the Polo family, the MEK/STE7 family, the PAK/STE20 family, the MEKK/STE11 family, the NimA family, the weel/mik1 family, the kinases involved in transcriptional control family, the Raf family, the Activin/TGF β receptor family, the flowering plant putative receptor kinases and close relatives family, the PSK/PTK leucine zipper domain family, the
30 casein kinase I family, the PKN prokaryotic protein kinase family and other OPK

protein kinase families. A large number of kinases are found in G. Hardie *et al.*, *Protein Kinase Facts Book* 0-12-324719-5 (1995).

Accordingly, a method of treating a kinase-implicated disease or condition in a mammal, preferably a human, comprises administration to the mammal of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula 1 and a pharmaceutically acceptable carrier. As used herein “therapeutically effective” includes alleviation of disease, disease symptoms, preventative, and prophylactic treatment.

Kinases are implicated in a large variety of diseases, as certain mutations in protein kinases can lead to activation of pathways causing, for example, the production of tumors, while other mutations in protein kinases block pathways and prevent a response. Some diseases that are linked to mutations in protein kinases are listed in the KinMutBase database (<http://www.uta.fi/imt/bioinfo/KinMutBase/>) (Stenberg et al., *Nucleic Acids Research*, Vol. 28, pp. 369-372, 2000). Diseases caused by protein kinase mutations include X-linked agammaglobulinemia (XLA), and non-insulin dependent diabetes mellitus (NIDDM), and severe combined immunodeficiency (SCID). Mutations related to tumor development have been linked to such diseases as Hirschprung’s disease, multiple endocrine neoplasia type 2 (MEN2) a and b, medullary thyroid carcinoma (FMTC), papillary renal carcinoma (HPRC), and Peutz-Jeghers syndrome.

Mutations in growth factor receptor kinases are linked to diseases such as mastocytosis, systemic mast cell disease, piebaldism, hypochondroplasia, thanatophoric dysplasia, and skeletal dysplasia. Other protein kinase-linked diseases include Coffin-Lowry syndrome, congenital insensitivity to pain with anhidrosis (CIPA), hypertension, vascular dysplasia, errors in vascular morphogenesis, and X-linked mental retardation. Mutations in protein kinases have also been linked to neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Alzheimer’s disease (AD).

Other diseases associated with protein kinases include Gaucher disease, hypochromic anemia, granulomatous disease, ataxia-telangiectasia, familial hypercholesterolemia, certain types of muscular dystrophy such as Driefuss-Emory

type, cystic fibrosis, type 1 hyperlipoproteinemia, Treacher Collins Franceschetti syndrome 1, Tay-Sachs disease, type 1 neurofibromatosis, adenomatous polyposis of the colon, X-linked ichthyosis, and Beckwith-Weidemann Syndrome.

Altered PKA (cyclic AMP-dependent protein kinase) expression is implicated in a
5 variety of disorders and diseases including cancer, thyroid disorders, diabetes, atherosclerosis, and cardiovascular disease. Altered MAP (mitogen-activated protein) kinase expression is implicated in a variety of disease conditions including cancer, inflammation, immune disorders, and disorders affecting growth and development. RTKs (receptor tyrosine kinases), CDKs and STKs (serine/threonine kinases) have all
10 been implicated in a host of pathogenic conditions including, significantly, large number of diverse cancers. Others pathogenic conditions that have been associated with PTKs include, psoriasis, hepatic cirrhosis, diabetes, atherosclerosis, angiogenesis, restinosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, autoimmune disease, and a variety of renal disorders.

15 Preferably, the conditions, diseases and/or disorders that can be affected using compounds of Formula 1 and compositions comprising such compounds include, but are not limited to, psoriasis, cancer (for example, chronic myelogenous leukemia, gastrointestinal stromal tumors, non-small cell lung cancer, breast cancer, ovarian cancer, recurrent ovarian cancer, prostate cancer such as hormonal refractory prostate
20 cancer, kidney cancer, head and neck cancer, or colorectal cancer), immunoregulation (graft rejection), atherosclerosis, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, diabetes (for example insulin resistance or diabetic retinopathy), septic shock, and the like.

In a preferred embodiment, the condition is cancer. A method of treating
25 cancer comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of Formulas 1, 2, or 3 and a therapeutically effective amount of an antitumor therapeutic. Treatment with the antitumor therapeutic may be prior to treatment with the inventive compounds, during treatment, following treatment with the compounds, or a combination thereof. Suitable antitumor
30 therapeutics are known, and are preferably a chemotherapeutic agent, for example mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, doxorubicin, or a

combination comprising at least one of the foregoing chemotherapeutic agents. Radiotherapeutic antitumor agents may also be used, alone or in combination with chemotherapeutic agents.

In another embodiment, pharmaceutical compositions comprising at least one
5 compound of Formula 1, together with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. Such pharmaceutical compositions include packaged pharmaceutical compositions for treating disorders responsive to modulation of kinase activity. A packaged pharmaceutical composition includes a container holding a therapeutically
10 effective amount of at least compound of Formula 1 and instructions (e.g., labeling) indicating that the contained composition is to be used for treating a disorder responsive to kinase modulation in the patient. Those of ordinary skill in the art will also recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water,
15 ethanol, mineral oil, vegetable oil, and dimethylsulfoxide (DMSO).

The compounds of Formula 1 may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like
20 is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or like injection or infusion techniques. The pharmaceutical compositions containing compounds of Formula 1 may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions,
25 dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to
30 provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients

that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and
5 lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

10 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

15 Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, which may be a naturally-
20 occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol
25 monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or
30 saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin, or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring, and coloring agents, may also be present.

Suitable pharmaceutical compositions for therapeutic use may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents

that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in
5 the preparation of injectables.

The compounds of general Formula 1 may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in
10 the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of Formula 1 may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics,
15 preservatives, and buffering agents can be dissolved in the vehicle.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It is convenient to formulate these animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its diet. It is also convenient to present the composition as a
20 premix for addition to the feed or drinking water.

Dosage levels of the order of from about 0.1 milligram to about 140 milligram per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 milligram to about 7 gram per human patient per day). The amount of active ingredient that may be combined with the carrier materials to
25 produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 milligram of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage
30 regimen of 4 times daily or less is preferred. For the treatment of eating disorders,

including obesity, a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of impotence a single dose that rapidly reaches effective concentrations is desirable. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the
5 specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

Preferred compounds of the invention will have certain pharmacological properties. Such properties include, but are not limited to oral bioavailability, low
10 toxicity, low serum protein binding, and desirable *in vitro* and *in vivo* half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of compounds used to treat peripheral disorders are often preferred.

Assays may be used to predict these desirable pharmacological properties. Assays
15 used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

20 Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (*Journal of Chromatography B* 1996, volume 677, pages 1-27).

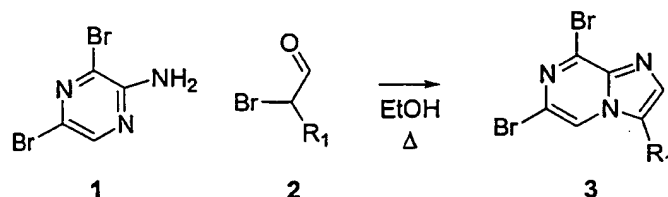
Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of
25 microsomal half-life as described by Kuhnz and Gieschen (*Drug Metabolism and Disposition* 1998, volume 26, pages 1120-1127).

In another embodiment, the compounds of Formula 1 are also useful as probes for the localization of kinases of therapeutic interest, that is, for both *in vivo* and *in vitro* identification and isolation the specific proteins to which it binds. A method for
30 identifying a kinase comprises contacting an organism, cell, or preparation comprising

the kinase with compound or salt according to Formulas 1, 2, or 3, and detecting modulation of an activity of the kinase. Suitable methods for detecting kinase modulation are known, for example those described herein.

The invention is further illustrated by the following non-limiting examples.

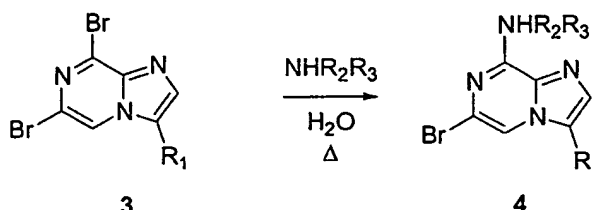
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Example 1. Synthesis of compounds of Formula 1 (FIGURE 1).

6,8-dibromoimidazo[1,2-a]pyrazine (3). A solution of 1.00 equivalents (eq.) of 3,5-dibromo-2-aminopyrazine 1 in ethanol is treated with 2.00 eq. of α -bromo-aldehyde 2 at room temperature (RT) and heated for 48 hours (hr). The solvent is removed under reduced pressure and the residue is triturated with diethyl ether and filtered to give the HBr salt 3.

8-Amino-6-bromoimidazo[1,2-a]pyrazine (4). Procedure 1: A mixture of 1.00 eq.

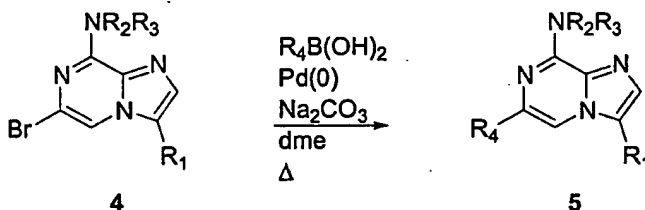


of 6,8-imidazo[1,2-a]pyrazine 3 in 28 % ammonia/water solution or 40% aqueous methyl amine is heated to between 80 to 90°C for 24 hr. The resulting mixture is partitioned between CH_2Cl_2 and H_2O . The aqueous layer is extracted with CH_2Cl_2 and the combined organic extracts are dried over Na_2SO_4 . The solvent is removed under reduced pressure and the resulting residue is crystallized from ethanol to yield 4.

Procedure 2: A solution of 1.00 eq. of 6,8-imidazo[1,2-a]pyrazine 3 in N,N-dimethylacetamide is treated with 2.00 eq. of benzylamine and 3.00 eq. of K_2CO_3 . The resulting mixture is heated to 100°C for 24 to 48 hours, cooled to RT and

20

partitioned between H₂O/CH₂Cl₂. The aqueous layer is extracted with CH₂Cl₂ and combined organic extracts are dried over Na₂SO₄. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (3:7 ethyl acetate (EtOAc)/Hexanes) to yield 4.



- 5 8-Amino-6-aryl-imidazo[1,2-a]pyrazine (5). A mixture of 1.00 eq. of 8-amino-6-bromoimidazo[1,2-a]pyrazine, 3.00 eq. of R₄-substituted boronic acid, and 0.10 eq. of Pd (PPh₃)₄, in 6.00 eq. of 1N Na₂CO₃/dme is heated to 90°C for 24 hr. The mixture is cooled to RT and partitioned between 10% acetic acid (AcOH)/CH₂Cl₂. The aqueous phase is extracted with CH₂Cl₂ and combined extracts are dried over Na₂SO₄.
- 10 The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (1-5% 2M NH₃/methanol/CH₂Cl₂) to yield 5.

Example 2. Synthesis of compounds of Formula 1b (FIGURE 2).

- 8-Amino-6-aryl-imidazo[1,2-a]pyrazine (6). A mixture of 1.00 eq. of 8-amino-6-bromoimidazo[1,2-a]pyrazine, 3.00 eq. of R₄-substituted boronic acid, and 0.10 eq. of Pd (PPh₃)₄, in 4.00 eq. of 1N Na₂CO₃/dme is heated to 90°C for 24 hr. The mixture is cooled to RT and partitioned between EtOAc/saturated NaHCO₃. The aqueous phase is extracted with EtOAc and the combined extracts are dried over Na₂SO₄. The solvent is removed under reduced pressure and the resulting residue is purified by
- 20 flash chromatography (1-5% 2M NH₃/methanol/EtOAc) to yield 6.

- N-[3-(8-Benzylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzamide (8). A solution of 1.00 eq. of 8-amino-6-aryl-imidazo[1,2-a]pyrazine in toluene/DMA is treated dropwise with 1.00 eq. of aryl acid chloride and stirred at RT for 10 hr. The resulting mixture is partitioned between EtOAc/saturated NaHCO₃. The aqueous
- 25 phase is extracted with EtOAc and the combined extracts are dried over Na₂SO₄. The

solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (1-5% methanol/EtOAc) to yield 8.

N-[3-(8-Benzylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-benzenesulfonamide (9). A solution of 1.00 eq. of 8-amino-6-aryl-imidazo[1,2-a]pyrazine in 5% N-methyl morpholine (NMM)/toluene is treated dropwise with 1.1 eq of aryl sulfonyl chloride and heated to 50°C for 8 h. The solution is cooled to RT and partitioned between EtOAc/saturated NaHCO₃. The aqueous phase is extracted with EtOAc and the combined extracts are dried over Na₂SO₄. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography ((1-5% methanol/EtOAc) to yield 9.

1-[3-(8-Benzylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-3-phenyl-urea (10). A solution of 1.00 eq. of 8-amino-6-aryl-imidazo[1,2-a]pyrazine in 5% NMM/toluene is treated dropwise with 1.0 eq of aryl isocyanate and heated to 60°C for 8 hr. The solution is cooled to RT and partitioned between EtOAc/saturated NaHCO₃. The aqueous phase is extracted with EtOAc and the combined extracts are dried over Na₂SO₄. The solvent is removed under reduced pressure and the resulting residue is purified by flash chromatography (1-5% 2M NH₃/MeOH/EtOAc) to yield 10.

Example 3. The following compounds were prepared in accordance with FIGURES 1 and 2 using the above procedures.

- (a) 1-(4-Chloro-phenyl)-3-[3-(8-methylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF=C₂₀H₁₇ClN₆O, MW=392.84 Mass Spec m/z (M⁺ +1) 393.06.
- (b) 1-(4-Chloro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF = C₂₅H₁₉ClN₆O MW=454.91 Mass Spec m/z (M⁺ +1) 455.04.
- (c) 1-(4-Chloro-phenyl)-3-{3-[8-(4-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=C₂₅H₁₈Cl₂N₆O, MW=489.36 Mass Spec m/z (M⁺ +1) 489.20.

- (d) 1-(4-Chloro-phenyl)-3-{3-[8-(3-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=C₂₅H₁₈Cl₂N₆O, MW=489.36 Mass Spec m/z (M⁺+1) 489.13.
- 5 (e) 1-(4-Chloro-phenyl)-3-{3-[8-(2-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=C₂₅H₁₈Cl₂N₆O, MW=489.36 Mass Spec m/z (M⁺+1) 489.04.
- (f) 1-(4-Chloro-phenyl)-3-{3-[8-(pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=C₂₄H₁₈ClN₇O, MW=455.90 Mass Spec m/z (M⁺+1) 456.07.
- 10 (g) 1-{3-[8-(4-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea, MF=C₂₆H₂₀Cl₂N₆O, MW=503.38 Mass Spec m/z (M⁺+1) 503.04.
- (h) 1-{3-[8-(3-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea, MF=C₂₆H₂₀Cl₂N₆O, MW=503.38 Mass Spec m/z (M⁺+1) 503.01.
- 15 (i) 1-{4-[8-(4-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea, MF=C₂₆H₂₀Cl₂N₆O, MW=503.38 Mass Spec m/z (M⁺+1) 503.01.
- (j) 1-{4-[8-(3-Chloro-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chloro-phenyl)-urea, MF=C₂₆H₂₀Cl₂N₆O, MW=503.38 Mass Spec m/z (M⁺+1) 503.01.
- 20 (k) 4-(6-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester, MF= C₂₈H₂₃ClN₆O₃, MW= 526.97 Mass Spec m/z (M⁺+1) 527.05.
- 25 (l) Cyclopropylmethyl-[6-(4-phenoxy-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine, MF=C₂₂H₂₀N₄O, MW=356.42 Mass Spec m/z (M⁺+1) 357.19.
- (m) (2-Methoxy-benzyl)-[6-(4-phenoxy-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine, MF= C₂₆H₂₂N₄O₂, MW= 422.48 Mass Spec m/z (M⁺+1) 423.19.

- (n) Benzo[1,3]dioxol-5-ylmethyl-[6-(4-phenoxy-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine, MF= C₂₆H₂₀N₄O₃, MW= 436.46 Mass Spec m/z (M⁺ +1) 437.18.
- (o) [6-(4-Chloromethyl-phenyl)-imidazo[1,2-a]pyrazin-8-yl]-(2-methoxy-benzyl)-amine, MF= C₂₁H₁₉ClN₄O, MW= 378.85 Mass Spec m/z (M⁺ +1) 379.13.
- 5 (p) 1-{4-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-phenyl-urea, MF= C₂₇H₂₄N₆O₂, MW= 464.52 Mass Spec m/z (M⁺ +1) 465.07.
- (q) (2-Methoxy-benzyl)-{6-[4-(4-methoxy-benzylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-yl}-amine, MF= C₂₈H₂₇N₅O₂, MW= 465.55 Mass Spec m/z (M⁺ +1) 466.10.
- 10 (r) (2-Methoxy-benzyl)-{6-[3-(4-methoxy-benzylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-yl}-amine, MF= C₂₈H₂₇N₅O₂, MW= 465.55 Mass Spec m/z (M⁺ +1) 466.09.
- (s) 1-{3-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-phenyl-urea, MF= C₂₇H₂₄N₆O₂, MW= 464.52 Mass Spec m/z (M⁺ +1) 465.05.
- 15 (t) 1-(2-Chloro-phenyl)-3-{4-[8-(2-methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF= C₂₇H₂₃ClN₆O₂, MW= 498.96 Mass Spec m/z (M⁺ +1) 499.18.
- (u) 1-{4-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(2-methoxy-phenyl)-urea, MF= C₂₈H₂₆N₆O₃, MW= 494.54 Mass Spec m/z (M⁺ +1) 495.22.
- 20 (v) 1-{4-[8-(2-Methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-methoxy-phenyl)-urea, MF= C₂₈H₂₆N₆O₃, MW= 494.54 Mass Spec m/z (M⁺ +1) 495.21.
- (w) 4-{6-[4-(Piperidine-1-carbonyl)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester, MF= C₂₇H₂₇N₅O₃, MW= 469.54 Mass Spec m/z (M⁺ +1) 470.08.
- 25 (x) 4-(6-{3-[3-(4-Chloro-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester, MF= C₂₈H₂₃ClN₆O₃, MW= 526.97 Mass Spec m/z (M⁺ +1) 527.05.

- (y) 4-(6-{3-[3-(2-Methylsulfanyl-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester, MF=C₂₉H₂₆N₆O₃S, MW=538.62 Mass Spec m/z (M⁺ +1) 539.18.
- 5 (z) {4-[8-(4-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-piperidin-1-yl-methanone, MF=C₂₄H₂₂ClN₅O, MW=431.92 Mass Spec m/z (M⁺ +1) 432.03.
- (aa) {4-[8-(2-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-piperidin-1-yl-methanone, MF=C₂₄H₂₂ClN₅O, MW=431.92 Mass Spec m/z (M⁺ +1) 432.03.
- 10 (bb) 3-Methoxy-N-{4-[8-(2-methoxy-benzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide, MF=C₂₈H₂₅N₅O₃, MW=479.53 Mass Spec m/z (M⁺ +1) 479.99.
- 15 (cc) 1-(3-Chloro-4-fluoro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF=C₂₅H₁₈ClFN₆O, MW= 472.90 Mass Spec m/z (M⁺ +1) 473.01.
- (dd) 1-(4-Chloro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF=C₂₅H₁₉ClN₆O, MW=454.91 Mass Spec m/z (M⁺ +1) 455.04.
- 20 (ee) 1-[3-(8-Phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea, MF=C₂₆H₁₉F₃N₆O, MW=488.46 Mass Spec m/z (M⁺ +1) 489.01.
- (ff) 1-(2-Chloro-5-trifluoromethyl-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea, MF=C₂₆H₁₈ClF₃N₆O, MW=522.91 Mass Spec m/z (M⁺ +1) 523.11.
- 25 (gg) 1-(4-Chloro-phenyl)-3-{3-[8-(4-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=C₂₅H₁₈Cl₂N₆O, MW=489.36 Mass Spec m/z (M⁺ +1) 489.20.

- (hh) 1-{3-[8-(4-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-trifluoromethyl-phenyl)-urea, MF=C₂₆H₁₈ClF₃N₆O, MW=522.91 Mass Spec m/z (M⁺ +1) 523.13.
- 5 (ii) 1-(3-Chloro-4-fluoro-phenyl)-3-{3-[8-(3-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=C₂₅H₁₇Cl₂FN₆O, MW=507.35 Mass Spec m/z (M⁺ +1) 507.13.
- (jj) 1-(4-Chloro-phenyl)-3-{3-[8-(3-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=C₂₅H₁₈Cl₂N₆O, MW=489.36 Mass Spec m/z (M⁺ +1) 489.13.
- 10 (kk) 1-{3-[8-(3-Chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-trifluoromethyl-phenyl)-urea, MF=C₂₆H₁₈ClF₃N₆O, MW=522.91 Mass Spec m/z (M⁺ +1) 523.12.
- (ll) 1-(3-Chloro-4-fluoro-phenyl)-3-{3-[8-(2-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea, MF=C₂₅H₁₇Cl₂FN₆O, MW=507.35
- 15 Mass Spec m/z (M⁺ +1) 507.09.

Example 4. A generalized description the standard AKT-1 Kinase Assay that may be used to evaluate the inventive compounds is as follows.

- In a final reaction volume of 40 microliters (μl), active recombinant N-terminus
- 20 his-tagged AKT-1/PKBα kinase expressed in Sf21 cells (UBI # 14-276; 50-100 nanogram; 19-38 nanomolar; about 4.5-9 mU) was incubated in 25 mM Tris pH 7.6; 5 mM Beta-glycerophosphate; 2 mM DTT; 100 μM sodium vanadate; 10 mM MgCl₂ in 96-well Pierce Reaci-Bind™ streptavidin-coated high binding capacity coated white plate (Pierce # 15502) coated with saturating amounts of biotinylated Crosstide
- 25 peptide (UBI #12-385; biotin-KGSGSGRPRPTSSFAEG; 50 picomoles; about 1.25 μM) and initiated with the addition of 2.5 μCi ³²P-γATP (specific activity 3000 Ci/mmole; 10 mCi/ml; about 21 nM). Compounds were tested initially in duplicate wells for determination of initial IC₅₀ inhibition in half log serial dilutions starting at 100 μM with a final concentration of 2% DMSO. Following a 30 min incubation at
- 30 30°C, the reaction was stopped by aspiration and 4 x 100 μl washes with TBS plus

0.05% Tween-20 prior to addition of 100 μ l scintillant and counting in Beckman TopCount instrument. Percent inhibition was calculated as $[1 - ((\text{AVE CPM}_{\text{compound}} - \text{AVE CPM}_{\text{no peptide background}}) / (\text{AVE CPM}_{\text{no compound MAX}} - \text{AVE CPM}_{\text{no peptide background}}))] * 100$]. Staurosporine, a general ATP competitive kinase inhibitor was used
5 as a reference compound and showed an IC₅₀ of approximately 60-100 nM for AKT-1 in the current assay format. Approximate S/N ratios are 8-12X with AVE CPM of Maximum about 15k and no peptide background about 1.5 K. Improved S/N ratios can be obtained using higher amounts of either AKT-1 kinase or ³²P- γ ATP. Cold ATP was not added in current format but has been added at up to 200 μ M in the
10 presence of 5 μ Ci ³²P- γ ATP resulting in S/N ratios of approximately 5-10X.

Example 5. A generalized description the standard assay to evaluate modulation of cell growth in soft agar (using cell lines HCT-15 (colon cancer), MiaPaca2 (pancreatic cancer), MCF-7 (breast cancer) and a NIH3T3 clone stably over-
15 expressing transfected myrAkt-1 human gene, for example) is as follows.

Preparation of the agar base layer: A quantity of 500 ml of 2X DMEM (phenol red free, Sigma Cat # D2902) is prepared, and sterile filtered. To that solution is added 10 ml of sodium pyruvate (Gibco, Cat # 11360-070), 10 ml of penicillin/streptomycin (Gibco, Cat# 15140-122), 10 ml of Glutamax (Gibco, cat# 33050-061) and 100 ml of
20 heat-inactivated FBS (Gemini) to make 2X DMEM complete media stock. Two stock concentrations of Sea Plaque low melt agar (Biowhittaker, Cat # 431097), 1%, and 0.6%, are prepared with ultra pure milliQ water, and sterilized by autoclaving. To prepare the agar base layer for a 12-well plate (Falcon # 353042), 6 ml of the 2X DMEM stock is mixed with 6 ml of 1% agar stock, both at 37°C, and 1 ml of the
25 resulting mixture is added to each well of the 12 well plate, 3 hrs prior to setup of top layer.

Top layer with cells and compound for evaluation: Cells at 60-80% confluency (log growth) in T75 are trypsinized with 1 ml of 1x trypsin solution (Gibco), neutralized with 10 ml of 1x DMEM 10% FBS and viable cells counted using a
30 hemocytometer via trypan blue exclusion. A working stock of 2.5×10^4 cells / ml is prepared in 1x DMEM 10% FBS. A 15 ml centrifuge tube is prepared for each

- concentration of compound tested in duplicate wells of a 12 well plate. The following are added in order: 1 ml of 2X DMEM stock at 37°C; compound at 2X final desired concentration (using 4 microliter volume from a 1000X concentrated dilution series in 100 % DMSO); followed by 2,500 cells (using 100 microliters of 1×10^4 cell /ml working stock), and finally 1 ml of 0.6 % agar stock at 37°C. Following careful mixing, 1 ml each is added to duplicate wells of the 12-well plate. The plate is then placed in a 37°C, 5% CO₂, humidified incubator for 10 to 14 days and read. Rapid diffusion of CPD throughout top and bottom agar layer results in final drug concentration of 1X.
- 10 Counting Colonies: After 10 days of incubation, the plates are removed from the incubator for photography and colony counting. Each well is scanned using an eyepiece with a micrometer guide and 5x phase optics. Colonies 50 micrometer or greater in diameter are scored as positive. Duplicate wells are averaged and percent inhibition calculated using number of colonies in no compound control wells as
- 15 100%.

All compounds described in Examples 1-3 were tested in accordance with the protocols of Examples 4-5 and determined to exhibit an IC₅₀ value less than or equal to 25 micromolar.

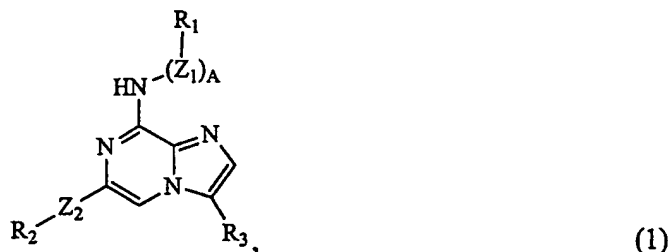
- 20 All cited references are incorporated herein in their entirety. While preferred embodiments have been shown and described, various modifications and substitutions may be made thereto without departing from the spirit and scope of the invention. Accordingly, it is to be understood that the present invention has been described by way of illustration and not limitations.

What is claimed is:

25

What is claimed is:

1. A compound having of Formula 1



a pharmaceutically acceptable salt, hydrates, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein

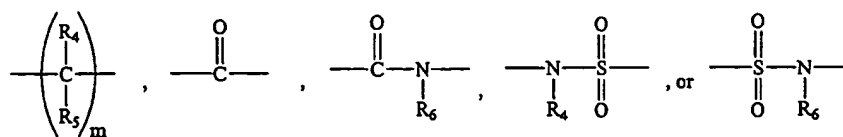
- 5 R_1 is hydrogen; cyclo-(C₃-C₆ alkyl)-methyl; straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains may form a 3 to 7 member heteroalkyl or alkyl ring; sulfonamide; C₁-C₆ alkoxy; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; mono- or di(C₁-C₆ alkyl)amino; mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl); or phenyl or heteroaryl ring which may be unsubstituted, or mono-, di- or trisubstituted with one or
10 more of hydroxy, nitro, cyano, amino, sulfonamide, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl); and,

- R_2 is straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains may form a 3-7 member heteroalkyl or alkyl ring; cyclo-(C₃-C₆ alkyl)-methyl;
15 C₁-C₆ alkoxy, except when Z₂ is phenylene and A is 0 and R_1 is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen, or when A is 1 and Z₁ is -C(R₄)(R₅)- wherein m is 1, 2, or 3 and R_1 is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆
20 alkoxy, or halogen, or when Z₂ is phenylene, A is 1, Z₁ is -C(R₄)(R₅)- wherein m is 1, 2, or 3, and R_1 is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen, or when Z₂ is -C(R₇)(R₈)- wherein n is 1, 2, or 3, each occurrence of R₇ and R₈ is independently straight or branched chain C₁-C₆ alkyl or halogen and R₂ is C₁-C₆
25 alkoxy or phenyl substituted with nitro; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; or phenyl or heteroaryl which may be unsubstituted, mono-, di- or trisubstituted with one or

more of hydroxy, nitro (except when Z_2 is phenylene and A is 0 and R_1 is straight or branched chain C_1 - C_7 alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C_1 - C_6 alkoxy, or halogen, or when A is 1 and Z_1 is $-C(R_4)(R_5)-$ wherein m is 1, 2, or 3, and R_1 is straight or branched chain C_1 - C_7 alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C_1 - C_6 alkoxy, or halogen, or when Z_2 is phenylene and A is 1 and Z_1 is $-C(R_4)(R_5)-$ wherein m is 1, 2, or 3, and R_1 is straight or branched chain C_1 - C_7 alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C_1 - C_6 alkoxy, or halogen, or when Z_2 is $-C(R_7)(R_8)-$ wherein n is 1, 2, or 3, each occurrence of R_7 and R_8 is independently straight or branched chain C_1 - C_6 alkyl or halogen and R_2 is C_1 - C_6 alkoxy or phenyl substituted with nitro), cyano, amino, halogen, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, $(C_1$ - C_6)-alkyl-oxy- $(C_1$ - C_6)alkoxy, mono- or di(C_1 - C_6 alkyl)amino, or amino(C_1 - C_6 alkyl); phenoxy phenyl where each phenyl may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, $(C_1$ - C_6)-alkyl-oxy- $(C_1$ - C_6)alkoxy, mono- or di(C_1 - C_6 alkyl)amino, or amino(C_1 - C_6 alkyl); phenyl or heteroaryl piperazine where the phenyl or heteroaryl ring may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, $(C_1$ - C_6)-alkyl-oxy- $(C_1$ - C_6)alkoxy, mono- or di(C_1 - C_6 alkyl)amino, or mono- or di(C_1 - C_6 alkyl)amino(C_1 - C_6 alkyl);

R_3 is hydrogen; straight or branched chain C_1 - C_7 alkyl, in which the branched alkyl chains may form a 3-7 member heteroalkyl or alkyl ring;

Z_1 is



wherein

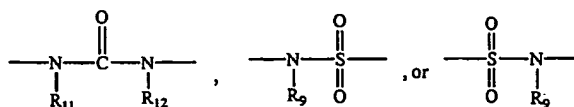
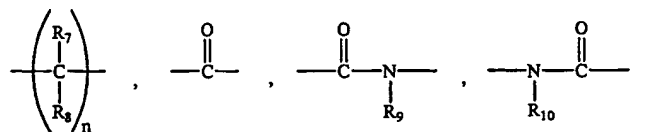
5 A is 0 or 1;

each occurrence of R_4 and R_5 is independently hydrogen, straight or branched chain C_1 - C_6 alkyl, sulfonamide, or halogen;

m is 0, 1, or 2; and

10 R_6 is hydrogen; straight or branched chain C_1 - C_6 alkyl; phenyl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, $(C_1$ - C_6)-alkyl-oxy- $(C_1$ - C_6)alkoxy, mono- or di- $(C_1$ - C_6 alkyl)amino, or amino(C_1 - C_6 alkyl); or heteroaryl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro,
15 cyano, amino, halogen, C_1 - C_6 alkyl, C_1 - C_6 perfluoroalkyl, C_1 - C_6 perfluoroalkoxy, C_1 - C_6 alkoxy, $(C_1$ - C_6)-alkyl-oxy- $(C_1$ - C_6)alkoxy, mono- or di- $(C_1$ - C_6 alkyl)amino, or amino(C_1 - C_6 alkyl); and

Z_2 is a divalent linking group selected from para-phenylene, meta-phenylene, ortho-phenylene, naphthylene,



20

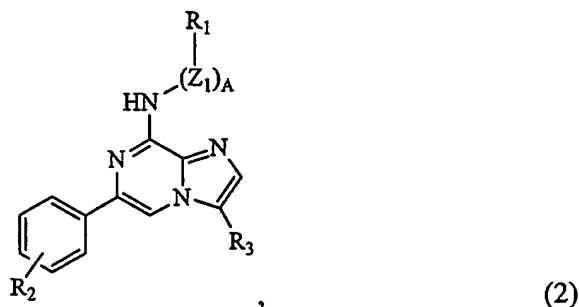
wherein

each occurrence of R₇ and R₈ is independently straight or branched chain C₁-C₆ alkyl, sulfonamide, or halogen;

n is 1, 2, or 3; and

5 R₉-R₁₂ are each independently hydrogen; straight or branched chain C₁-C₆ alkyl; phenyl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl); or
10 heteroaryl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl).

2. A compound having Formula 2



a pharmaceutically acceptable salt, hydrates, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein

- 5 R_1 is hydrogen; cyclo-(C₃-C₆ alkyl)-methyl; straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains are allowed to also form a 3-7 member heteroalkyl or alkyl ring; sulfonamide; C₁-C₆ alkoxy; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl); or phenyl or heteroaryl ring which may be unsubstituted, mono-, di- or
- 10 trisubstituted with one or more of hydroxy, nitro, cyano, amino, sulfonamide, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl);

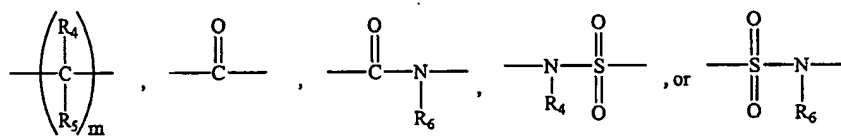
- R_2 in Formula 2 is straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains are allowed to also form a 3-7 member heteroalkyl or alkyl
- 15 ring; cyclo-(C₃-C₆ alkyl)-methyl; C₁-C₆ alkoxy except when A is 0 and R_1 is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen, or when A is 1 and Z₁ is -C(R₄)(R₅)- wherein m is 1, 2, or 3 and R_1 is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino,
- 20 C₁-C₆ alkoxy, or halogen; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; phenyl or heteroaryl which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro (except when A is 0 and R_1 is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen, or when A is 1 and Z₁ is -C(R₄)(R₅)- wherein m is 1, 2, or 3, and

R₁ is straight or branched chain C₁-C₇ alkyl (but not cycloalkyl), phenyl, or phenyl substituted with hydroxy, nitro, cyano, amino, C₁-C₆ alkoxy, or halogen), cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, amino(C₁-C₆ alkyl); phenoxy phenyl where each phenyl may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl); or phenyl or heteroaryl piperazine where the phenyl or heteroaryl ring may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl);

R₃ in Formula 2 may be hydrogen; straight or branched chain C₁-C₇ alkyl, in which the branched alkyl chains can also form a 3-7 member heteroalkyl or alkyl ring;

A in Formula 2 is 0 or 1; and

Z₁ in Formula 2 is



wherein

each occurrence of R₄ and R₅ is independently hydrogen, straight or branched chain C₁-C₆ alkyl, sulfonamide, or halogen;

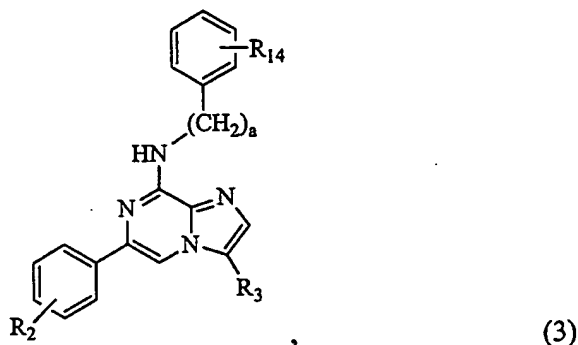
m is 1, 2, or 3; and

R₆ is hydrogen; straight or branched chain C₁-C₆ alkyl; phenyl, which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-

5

oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl); or heteroaryl, which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl).

3. A compound having Formula 3:



a pharmaceutically acceptable salt, hydrates, solvate, crystal form, diastereomer, prodrug, or mixture thereof, wherein

5 a is 0, 1, 2 or 3;

R_{14} is hydrogen; cyclo-(C₃-C₆ alkyl)-methyl; straight or branched chain C₁-C₆ alkyl, in which the branched alkyl chains may form a 3-7 member heteroalkyl or alkyl ring; sulfonamide; C₁-C₆ alkoxy; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; mono- or di(C₁-C₆ alkyl)amino, mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl); or phenyl or heteroaryl
 10 ring, which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, sulfonamide, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl);

R_2 in Formula 3 is straight or branched chain C₁-C₆ alkyl, in which the
 15 branched alkyl chains may form a 3-7 member heteroalkyl or alkyl ring; cyclo-(C₃-C₆ alkyl)-methyl; C₁-C₆ alkoxy except where R_1 is hydrogen, C₁-C₆ alkoxy, or phenyl substituted with nitro; (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy; phenyl or heteroaryl, which may be unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro, cyano, amino, halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-
 20 C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl); phenoxy phenyl, in which each phenyl may be independently unsubstituted, mono-, di- or trisubstituted with one or more of hydroxy, nitro (except where R_1 is hydrogen, C₁-C₆ alkoxy, or phenyl substituted with nitro), cyano, amino,

halogen, sulfonamide, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or amino(C₁-C₆ alkyl); or phenyl or heteroaryl piperazine, in which the phenyl or heteroaryl ring may be independently unsubstituted, mono-, di- or trisubstituted with
5 one or more of hydroxy, nitro, cyano, amino, halogen, sulfonamide, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, C₁-C₆ perfluoroalkoxy, C₁-C₆ alkoxy, (C₁-C₆)-alkyl-oxy-(C₁-C₆)alkoxy, mono- or di(C₁-C₆ alkyl)amino, or mono- or di(C₁-C₆ alkyl)amino(C₁-C₆ alkyl); and

R₃ is hydrogen; straight or branched chain C₁-C₆ alkyl, in which the branched
10 alkyl chains may form a 3-7 member heteroalkyl or alkyl ring.

4. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(4-chloro-phenyl)-3-[3-(8-methylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea.

5. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(4-chloro-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea.

6. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(4-chloro-phenyl)-3-{3-[8-(4-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

7. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(4-chloro-phenyl)-3-{3-[8-(3-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

8. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(4-chloro-phenyl)-3-{3-[8-(2-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

9. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(4-chloro-phenyl)-3-{3-[8-(pyridin-3-ylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

10. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{3-[8-(4-chlorobenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chlorophenyl)-urea.

11. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{3-[8-(3-chlorobenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chlorophenyl)-urea.

12. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{4-[8-(4-chlorobenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chlorophenyl)-urea.

13. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{4-[8-(3-chlorobenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(4-chlorophenyl)-urea.

14. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 4-(6-{3-[3-(4-chlorophenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester.

15. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is cyclopropylmethyl-[6-(4-phenoxyphenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine.

16. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is (2-methoxybenzyl)-[6-(4-phenoxyphenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine.

17. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is benzo[1,3]dioxol-5-ylmethyl-[6-(4-phenoxyphenyl)-imidazo[1,2-a]pyrazin-8-yl]-amine.

18. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is [6-(4-(chloromethyl)phenyl)-imidazo[1,2-a]pyrazin-8-yl]-(2-methoxy-benzyl)-amine.

19. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{4-[8-(2-methoxybenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-phenyl-urea.

20. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is (2-methoxy-benzyl)-{6-[4-(4-methoxybenzylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-yl}-amine.

21. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is (2-methoxy-benzyl)-{6-[3-(4-methoxybenzylamino)-phenyl]-imidazo[1,2-a]pyrazin-8-yl}-amine.

22. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{3-[8-(2-methoxybenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-phenyl-urea.

23. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(2-chloro-phenyl)-3-{4-[8-(2-methoxybenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

24. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{4-[8-(2-methoxybenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(2-methoxy-phenyl)-urea.

25. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{4-[8-(2-ethoxybenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-methoxy-phenyl)-urea.

26. A compound according to claim embodiment 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compounds is 4-{6-[4-(piperidine-1-carbonyl)-phenyl]-imidazo[1,2-a]pyrazin-8-ylamino}-benzoic acid ethyl ester.

27. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 4-(6-{3-[3-(4-chlorophenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester.

28. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 4-(6-{3-[3-(2-methylsulfanyl-phenyl)-ureido]-phenyl}-imidazo[1,2-a]pyrazin-8-ylamino)-benzoic acid ethyl ester.

29. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is {4-[8-(4-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-piperidin-1-yl-methanone.

30. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is {4-[8-(2-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-piperidin-1-yl-methanone.

31. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 3-methoxy-N-{4-[8-(2-methoxybenzylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-benzamide.

32. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(3-chloro-4-fluorophenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea.

33. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(4-chlorophenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea.

34. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-3-(3-trifluoromethyl-phenyl)-urea.

35. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(2-chloro-5-trifluoromethyl-phenyl)-3-[3-(8-phenylamino-imidazo[1,2-a]pyrazin-6-yl)-phenyl]-urea.

36. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(4-chlorophenyl)-3-{3-[8-(4-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

37. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{3-[8-(4-chloro-phenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-trifluoromethylphenyl)-urea.

38. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(3-chloro-4-fluorophenyl)-3-{3-[8-(3-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

39. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(4-chlorophenyl)-3-{3-[8-(3-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

40. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-{3-[8-(3-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-3-(3-trifluoromethylphenyl)-urea.

41. A compound as in claim 1, or a pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug thereof, wherein the compound is 1-(3-chloro-4-fluorophenyl)-3-{3-[8-(2-chlorophenylamino)-imidazo[1,2-a]pyrazin-6-yl]-phenyl}-urea.

42. A compound, pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug as in claims 1 to 41, wherein in an in vitro assay of kinase modulation, the compound exhibits a IC_{50} value less than or equal to 25 micromolar.

43. A compound, pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug as in claims 1 to 41, wherein in an in vitro assay of modulation of soft agar growth, the compound exhibits a IC_{50} value less than or equal to 25 micromolar.

44. A compound, pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug as in claims 1 to 41, wherein in an in vitro assay of modulation of soft agar growth, wherein the cells are HCT-15, MiaPaca-2, MCF-7, OVCAR-4, or A549 cells, the compound exhibits a IC_{50} value less than or equal to 25
5 micromolar.

45. A pharmaceutical composition comprising
a compound, pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug as in claims 1 to 41; and
at least one pharmaceutically acceptable carrier or excipient.

46. A method of treating a kinase-implicated condition in a mammal, comprising administering to the mammal a therapeutically effective amount of a compound, pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug claims 1 to 41.

47. The method of claim 46, wherein the mammal is a human.

48. The method of claim 46, wherein the mammal is a dog or cat.

49. A method of treating cancer, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound, pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug of claims 1 to 41.

50. A method of treating cancer, comprising administering to a mammal in need thereof a therapeutically effective amount of a compound, pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug of claims 1 to 41 and a therapeutically effective amount of an antitumor therapeutic.

51. The method of claim 50, wherein treatment with the antitumor therapeutic follows treatment with the compound, pharmaceutically acceptable salt, hydrate, solvate, crystal form, diastereomer, or prodrug of claims 1 to 41.

52. The method of claim 50, wherein the antitumor therapeutic is a chemotherapeutic agent.

53. The method of claim 52, wherein the chemotherapeutic agent is mitomycin C, carboplatin, taxol, cisplatin, paclitaxel, etoposide, doxorubicin, or a combination comprising at least one of the foregoing chemotherapeutic agents.

54. The method of claim 50, wherein the antitumor therapeutic is a radiotherapeutic agent.

55. The method of claim 50, wherein the mammal is a human.

56. The method of claim 50, wherein the mammal is a dog or cat.

57. A method for identifying a kinase, comprising contacting an organism, cell, or preparation comprising the kinase with a compound or salt according to claim 1, and detecting modulation of an activity of the kinase.

FIGURE 1

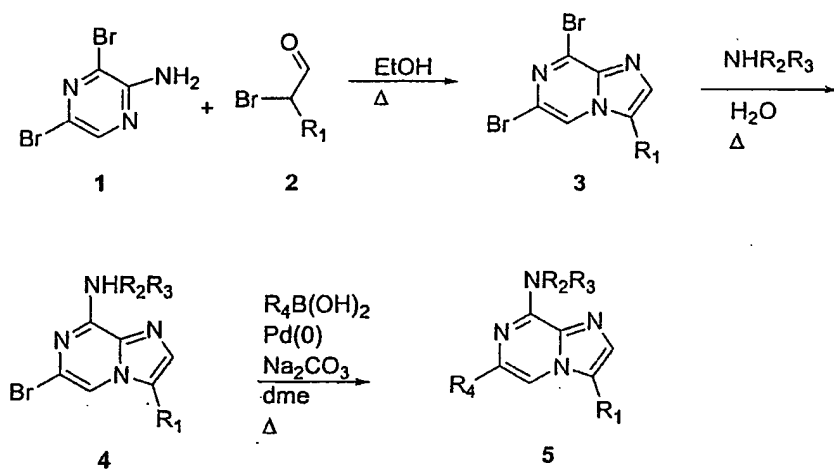
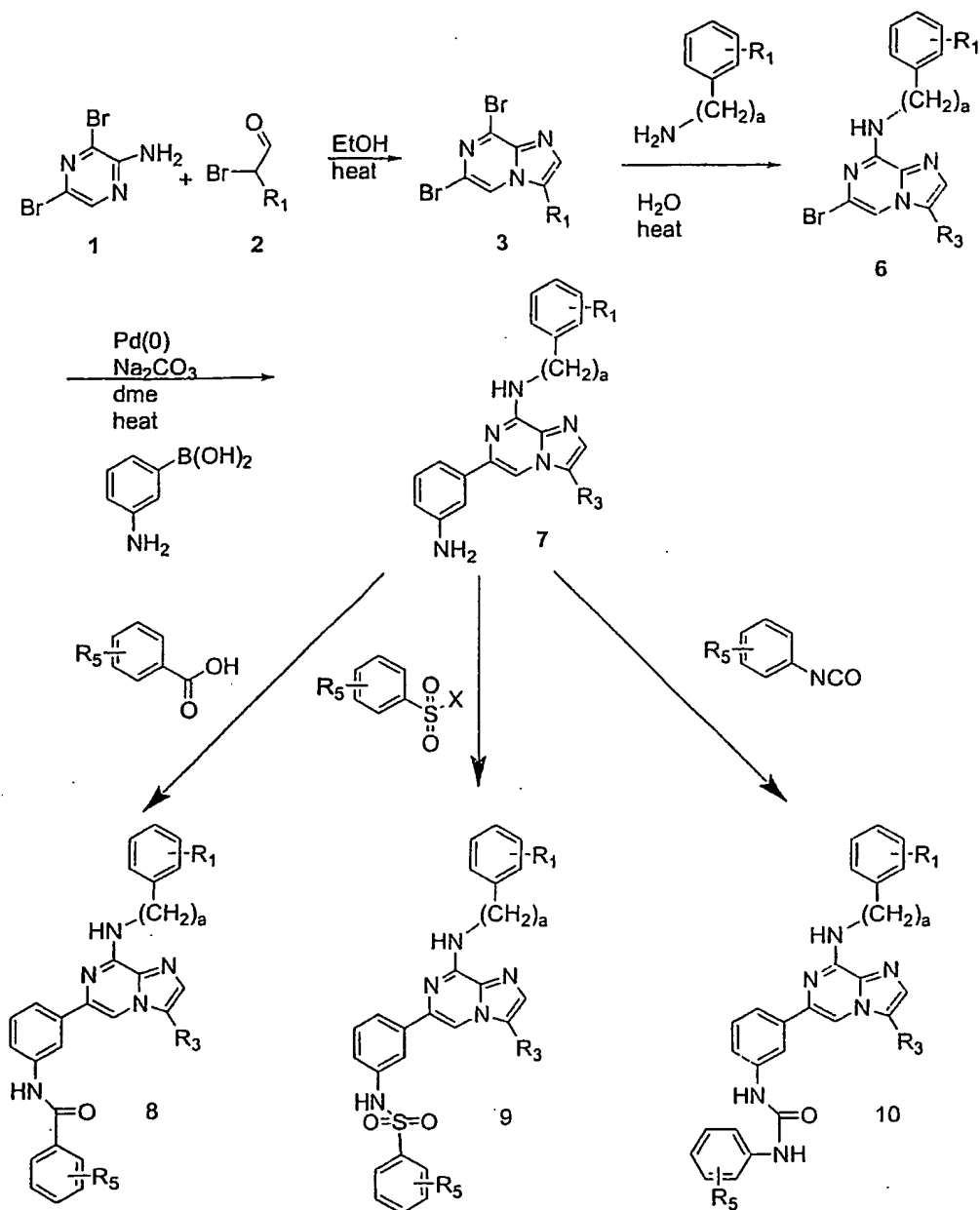


FIGURE 2



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
30 October 2003 (30.10.2003)

PCT

(10) International Publication Number
WO 2003/089434 A3

(51) International Patent Classification⁷: **C07D 487/04**,
A61K 31/4985, A61P 35/00 // (C07D 487/04, 241:00,
235:00)

(21) International Application Number:
PCT/US2003/012222

(22) International Filing Date: 21 April 2003 (21.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/374,213 19 April 2002 (19.04.2002) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ,
VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
15 January 2004

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: **IMIDAZO[1,2-a]PYRAZIN-8-YLAMINES METHOD OF MAKING AND METHOD OF USE THEREOF**

(57) Abstract: A novel composition comprises a compound of Formula 1 the pharmaceutically acceptable salts, hydrates, solvates, crystal forms, diastereomers, prodrugs, or mixtures thereof. The composition is of particular utility in the treatment of kinase-implicated disorders.



WO 2003/089434 A3

INTERNATIONAL SEARCH REPORT

International application No

PCT/US 03/12222

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/4985 A61P35/00 //(C07D487/04, 241:00, 235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 88 04298 A (BYK GULDEN LOMBERG CHEM FAB) 16 June 1988 (1988-06-16) claim 1	1
A	US 5 593 997 A (DOW ROBERT L ET AL) 14 January 1997 (1997-01-14) cited in the application claims 1,11-14,16	1,45,46
A	EP 0 480 713 A (MERCK & CO INC) 15 April 1992 (1992-04-15) claim 1	1
A	WO 99 28322 A (DAHLSTROEM MIKAEL; AMIN KOSRAT (SE); ASTRA AB (SE); NORDBERG PETER) 10 June 1999 (1999-06-10) claims 1,9	1
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

8 October 2003

Date of mailing of the international search report

22/10/2003

Name and mailing address of the ISA

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Hass, C

INTERNATIONAL SEARCH REPORT

International Publication No.:

PCT/US 03/12222

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	O. VITSE ET AL: "New Imidazo(1,2-a)pyrazine Derivatives with Brochodilatory and Cyclic Nucleotide Phosphodiesterase Inhibitory Activities" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 7, 1999, pages 1059-1065, XP002257093 cited in the application table 1	1
P,X	WO 02/060492 A (CYTOPIA PTY LTD; BURNS CHRISTOPHER JOHN (AU); WILKS ANDREW FREDERICK) 8 August 2002 (2002-08-08) cited in the application page 58, "Chemistry 70" claims 7-12, 24-29	1, 45, 46

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/12222

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-46, 49-51 (all partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 46-56 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claim 57 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 1-46, 49-51 (all partly)

Claims 1-46, 49-51: The scope of the group of compounds defined by the functional term "prodrug" is unclear within the meaning of Article 6 PCT, as it is not possible to assign a molecular structure to this group. Therefore it was not possible to carry out a complete search over the whole scope claimed. Consequently, the parts of the claims referring to "prodrug" have not been searched.

In claims 1-3, the disclaimers, starting with "except when" and containing the term "but not cycloalkyl", are formulated such that it cannot be unambiguously deduced from the claims which definitions belong to the disclaimers and which belong to the definition of subject-matter for which protection is sought. Here a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Moreover, it is not clear for which reason these disclaimers have been introduced so that it could not been verified completely which very compounds shall be excluded. Consequently, with regard to claims 1-3, the search has been carried out for those parts of the claims which do appear to be clear, namely the claims without considering the disclaimers, in conjunction with concrete examples and compounds mentioned in the description.

Present claim 44 relates to a compound defined by reference to a desirable characteristic or property, namely that the compound has a specific IC50 value in an in vitro assay of modulation of soft agar growth, comprising specific cells. The claim does not say how such desirable property could be achieved. Claim 44 covers all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. Consequently, the search has been carried out for those parts of the claim which appear to be clear, supported and disclosed, namely those parts relating to the compounds disclosed in example 3 of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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